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Via E-mail to: lunn@niehs.nih.gov

Dr. Ruth Lunn
Director, Office of the Report on Carcinogens
DNTP, NIEHS
P.O. Box 12233, MD K2-14
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Re: Proposed National Toxicology Program (NTP) Review Process for the Report on Carcinogens: Request for Public Comment and Listening Session, 76 Federal Register 67200 (October 31, 2011)

Dear Dr. Lunn:

On behalf of the Nickel Institute, I am making this submission in response to the National Toxicology Program's (NTP's) request for public comment on the proposed review process for the Report on Carcinogens (RoC). The Nickel Institute is an association of worldwide nickel producing companies representing ~90 percent of global nickel production. NTP's review of the RoC process is timely. We hope the suggestions offered in these Comments will help improve the current process and strengthen the scientific basis of NTP's listing decisions.

Comments on the Proposed RoC Review Process

In its proposal, NTP describes a four-step process.

In Step 1, candidate substances are selected and added to the list of candidate substances for RoC evaluation.

In Step 2, the Office of the Report on Carcinogens (ORoC) prepares a draft RoC Monograph and circulates it to NTP's partner agencies – after which a "revised draft RoC Monograph" is prepared for public comment and peer review. Importantly, the proposed process seems to contemplate that during Step 2, NTP *may* – but apparently need not – solicit external scientific input and/or public comment on the draft RoC Monograph and on the scientific issues relevant to assessing the potential carcinogenicity of the candidate substance. This procedure is not adequate to ensure meaningful public participation.

Solicitation of written public comments on the draft RoC Monograph during Step 2 should be *mandatory*, not discretionary – because the "revised draft RoC Monograph" developed during Step 2 drives the listing determination. Accordingly, an opportunity for public input at this stage of the process is critical – because, once it emerges from Step 2, the "revised draft RoC Monograph" will essentially be a *fait accompli* that is unlikely to be changed based on comments received or considered in subsequent stages of the process. By the same token, it would be desirable for NTP to approach independent scientists who have special expertise

with the candidate substance to review and comment on the draft RoC Monograph before the "revised" version is prepared and moved forward to Step 3.

In Step 3, NTP releases the "revised draft RoC Monograph" for public comment and convenes an external advisory group – the Board of Scientific Counselors (BSC) or an expert panel – to peer review the document.[1] Interested members of the public may submit written comments during Step 3 and may attend the peer review meeting where they can provide oral comments. This latter opportunity to interact directly with the peer reviewers can be very important – but only if two conditions are met: (1) Public comments must be furnished to the peer reviewers sufficiently in advance of the meeting as to allow them to read and understand the points being made; and (2) Scientific experts representing members of the public must be given an adequate opportunity to engage in a meaningful interchange with the peer reviewers at the public meeting. Past experience suggests that these conditions often are not met – with the result that the opportunity to provide oral comments to the peer reviewers is far less valuable than it should be.

Following the peer review meeting, a "peer-review report" is prepared and posted on the RoC website. NTP does not say whether public comments received during Step 3 are similarly posted. They should be.

At this point, the "ORoC considers the peer-review report in concert with the NTP Director, . . . finalizes the revised draft RoC Monograph [and] prepares a response to the peer-review report that is released to the public when the next edition of the RoC is released." This procedure raises several questions.

- First, is the Monograph revised once again to reflect peer review and public comments? If not, what is the rationale for leaving it unchanged?

- Second, why is NTP's response to the peer review report not released to the public until the next edition of the RoC is released? The peer review report itself is posted on the RoC website as soon as it is prepared. A parallel approach should be followed in the case of NTP's response to the report.

- Third, why does ORoC not prepare a response to public comments? If the "revised draft RoC Monograph" that emerges from Step 2 is not further revised to reflect significant public comments, the public has a right to know why.

In Step 4, which occurs biannually, the Secretary of HHS (following consideration by the NTP Executive Committee) reviews and decides whether to approve the recommended listing status of the candidate substances. Those that are approved are then added to the RoC – at which point, the public is notified of the listing outcome, and NTP's response to the peer-review report is posted on the RoC website. Our only comment here is that NTP's response to the peer-review report should be posted on the website earlier – *i.e.*, during Step 3 when it is prepared.

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[1] How an expert panel will be selected is not stated. This obviously is an important point that would benefit from clarification.

Comments on Related Matters

In addition to the foregoing observations regarding the proposed RoC review process, we would like to offer some thoughts on three issues relating to the listing criteria and the discussions of listed substances that appear in the body of the RoC.

(1) Route of Exposure:

The RoC listing criteria should be revised to place a greater emphasis on whether the candidate substance poses a carcinogenic hazard via routes of exposure that are relevant to the U.S. population. Under Section 301(b)(4) of the Public Health Service Act, as amended, the RoC is supposed to address known or reasonably anticipated carcinogens "to which a significant number of persons residing in the United States are exposed." Obviously, the concern is with those exposures of the U.S. population that present a potential risk of cancer. If a substance has been associated with an increased cancer risk only via a route of exposure that has no relevance for U.S. residents (*e.g.*, injection site tumors in rats), while studies via relevant routes of exposure (*i.e.*, inhalation, ingestion, and dermal contact) indicate the absence of a carcinogenic hazard, the substance – for all practical purposes – would not present a "known" or "reasonably anticipated" cancer hazard to persons residing in the United States. In our view, including such a substance in the RoC is misleading.

NTP seems to recognize this point – at least implicitly – since the listing criteria assert that conclusions regarding carcinogenicity are based, *inter alia*, on information regarding route of exposure. In practice, however, the significance of route of exposure is often slighted or ignored. While it may be prudent to act on the basis of injection-induced tumors when studies by relevant routes of exposure are lacking, we believe that, in general, studies by relevant routes of exposure should take precedence over those conducted by a less relevant route when results from both types of studies are available. And, when there are both positive and negative (or "non-positive") studies of similar quality, the non-positive studies should be equally considered and described in the RoC. At present, this is not always the case. NTP's failure to place proper emphasis on route of exposure and to present a balanced view of both negative and positive studies undercuts Congress' objective in directing publication of the RoC (*i.e.*, to identify cancer hazards associated with actual exposures of U.S. residents), and it does a disservice to readers of the document.

To remedy this problem, the RoC listings should specify, where appropriate, the route(s) of exposure of the chemical to which the classification applies and those for which the classification is inapplicable or uncertain. By the same token, the substance profile for the chemical that appears in the RoC should discuss whether a carcinogenic hazard has been found in studies involving each of the three principal routes of human exposure to the chemical (inhalation, oral ingestion, and dermal contact). This would provide much needed perspective for readers of the RoC and would avoid giving rise to concerns that are not justified by the nature of exposures in the U.S.

(2) Physical Form of the Substance:

As with route of exposure, the RoC listings should specify, where appropriate, the physical form(s) of the substance to which the classification applies and those for which the classification is inapplicable or uncertain. A good illustration of this would be powder forms of a substance which might be carcinogenic via inhalation versus massive forms of the same substance which cannot be inhaled and, therefore, would not be carcinogenic (*e.g.*, nickel-plated products). Currently, this distinction is not made in the RoC. Where the physical form of a chemical is relevant to its carcinogenic potential, that fact should be reflected both in the listings themselves (by specifying the form of the chemical to which the listing applies) and in the substance profile for the chemical.

(3) Speciation:

Finally, we urge NTP to be more attentive to species-specific differences in assessing the carcinogenic potential of a chemical group, such as the compounds of a particular metal. There can be significant differences in the ability of different compounds to release the critical metal ion in a manner and with a valence state that makes it available to interact with target sites inside the cell nucleus. Often the available information may not be sufficient to make distinctions among species of a metal for purposes of hazard classification. But in those cases where adequate species-specific information is available, an effort should be made to present the evidence separately for different forms of a metal.

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We appreciate your consideration of these Comments. If you have any questions, please let me know. I can be reached by telephone at (301) 469-0029 or by e-mail at neiljking@verizon.net.

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Very truly yours,

[Redacted]

Neil King
Counsel to the Nickel Institute